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A Comparative QSAR Study on 2-Amino-6-arylsulfonylbenzonitrile Analogues as Non-nucleoside Reverse Transcriptase Inhibitors of HIV-1

NILANJANA PANCHOLI and NITIN S. SAPRE*
School of Chemical Sciences, Devi Ahilya University Indore-452001, India
Tel: (91)(731)4067958
E-mail: sukusap@yahoo.com, nsapre.schem@dauniv.ac.in

In this study we have investigated the relative correlation potential of Wiener (W), Randic (χ), Balaban (J) and Szeged (Sz) indices in developing quantitative structure-activity relationships QSAR; log(1/IC_{50}) values of 2-amino-6-arylsulfonylbenzonitrile analogues are used for this purpose. The statistical analyses for univaraite and multivariate correlations have indicated that W and Sz are closely related to connectivity index χ and that the W, χ and Sz indices have similar correlation potentials. Sz index gives better result than both W and χ. Other index, J, correlate poorly with the log(1/IC_{50}) values. Substitution effect of halogens is studied by incorporating indicator parameter, IPXR, in performing correlations. The correlations have indicated that all indices combined with indicator parameter give the best result and also that the presence of a halogen substitutions adversely affect the log(1/IC_{50}) value.

Key Words: QSAR study, 2-Amino-6-arylsulfonylbenzonitrile, Analogues, Transcriptase, Inhibitors, HIV-1.

INTRODUCTION

Acquired immuno deficiency syndrome (AIDS) is a vandemic disease whose etiologic agent is human immuno deficiency virus type-1 (HIV-1). The etiologic agent of AIDS infects, the cells of the immune system leading to destruction of host immunity, generally the CD-4 helper T-cells. There are three viral enzymes related to HIV namely: HIV-Protease, HIV-Integrase and HIV-Reverse transcriptase. The reverse transcriptase enzyme is an important target for development of selective inhibitors. The HIV reverse transcriptase inhibitors are of two types: Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). The safety, selectivity and high potency of NNRTIs have made them more important as compared to NRTIs[1-3].

Structurally diverse NNRTIs such as quinoxaline derivatives (efavirenz)[4], hydroxyethoxyphenylthiothymine (HEPT)[5], 2',5'-*bis*(O-(*tert*-butyldimethylsilyl)-3'-spiro-5''-(4''-amino-1'', 2''-oxathiole-2'', 2''-dioxide) pyrimidine (TSAO) derivatives[6], α-anilinophenylacetamide (α-APA) derivatives[7], phenylethylthioureathiazole (PETT)[8], tetrahydroimidazobenzodiazepinone (TIBO)[9], dipyridodiazepinone (Nevirapine)[10], bis(heteroaryl) piperazine derivatives (BHAP) (Delavirdine)[11], have been reported in literature and of these nevirapine, delavirdine and efavirenz have been approved for the treatment of HIV-1 infection.

The NRTIs act at the catalytic site of HIV-RT by terminating DNA synthesis[12] while NNRTIs inhibit the enzyme non-competitively to a site adjacent to deoxyribonucleoside triphosphate binding site of enzyme[13-15]. The adjacent site is approximately 10 Å away from the catalytic site. Due to rapid development of drug resistance, mutation effectivity of NNRTIs is produced[16]. As is known that side chain and backbone of residue surrounding the pocket, adjust to each bound drug in a common fashion. These conclude that this protein is able to accommodate inhibitors of different chemical structures.

NNRTIs of a new ring system containing 2-amino-6-arylsulfonylbenzonitriles are found to effectively inhibit the replication of a variety of HIV-1 strains at the reverse transcriptase step[17]. It is required to have a precise and detailed understanding of the important structure-activity relationships (SAR). Therefore the quantitative structure activity relationship (QSAR) based on topological indices, increasingly being used in several areas of chemistry, biochemistry, pharmacology and environmental research, is performed on AASBN derivatives[18,19].

In these methods the molecules are mathematically encoded according to their structural features. The conversion of a chemical structure into a mathematical number (numerical value) often can be achieved in varied ways[20-23].

It appears that among many topological indices[24-35] that have been proposed since the Wiener index (W)[25] introduced by Wiener, the Randic connectivity index (χ)[31] introduced by Randic, the Balaban index (J)[36] introduced by Balaban and the Szeged index (Sz)[37] introduced by Gutman, are the most often used indices in QSAR and QSPR.

In earlier work[38] we have reported a comparative study of the Wiener, Szeged and Randic Connectivity indices for a sample of derivatives of benzoic acids. In present work a series of 53 compounds of 2-amino-6-arylsulfonylbenzonitriles is taken and biological activity ($\log(1/IC_{50})$ of 2-amino-6-arylsulfonylbenzonitriles[17] are correlated with Wiener[25], Randic[31], Balaban[36] and Szeged[37] indices (topological indices). The univariate as well as multivariate correlations have demonstrated that these indices have a

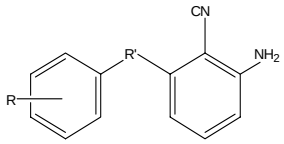
good correlation potential in developing QSAR. Here, we have also considered the indicator parameter IPXR (dummy parameters) for understanding the substitutent effect, which has improved the correlation coefficient. The results are discussed below.

EXPERIMENTAL

In the present work QSAR study has been performed with aims of: (**A**) Determining Quantitative Structure Activity Relationship (QSAR) and structural requirements of HIV-1 NNRTIs in the class of 2-amino-6-arylsulfonylbenzonitrile derivatives, (**B**) Obtaining information about the structural characteristics underlying the inhibition of this class of compounds.

All the 53 chemical structures of 2-amino-6-arylsulfonyl benzonitrile derivatives are illustrated in Table-1 together with their biological activities, the dependent variable was scaled by natural logarithm as the values differed by several orders of magnitude, expressed as $\log(1/IC_{50})$, where IC_{50} is the inhibitory concentration of a compound required to achieve 50% reduction in the cytopathic effect of HIV-1 on MT-4 cells.

TABLE-1
ANTI-HIV-1 ACTIVITY AND INHIBITORY CONCENTRATION ($\log(1/IC_{50})$), TOPOLOGICAL INDICES OF 2-AMINO-6-ARYLSULFONYLBENZONITRILE (AASBN) ANALOGUES



Comp. No.	R	R'	IC_{50}	log ($1/IC_{50}$)	W	χ	J	Sz	IPXR
1	H	S	8.70	-0.9395	609.00	8.7196	1.9189	941.00	0.00
2	2-OCH_3	S	2.70	-0.4314	802.00	9.6682	1.9826	1210.00	0.00
3	3-OCH_3	S	1.50	-0.1761	826.00	9.6514	1.9234	1258.00	0.00
4	3-CH_3	S	0.96	0.0177	708.00	9.1134	1.9308	1090.00	0.00
5	4-CH_3	S	5.70	-0.7559	720.00	9.1134	1.9066	1114.00	0.00
6	2-Cl	S	7.20	-0.8573	696.00	9.1302	1.9652	1066.00	1.00
7	3-Cl	S	16.00	-1.2041	708.00	9.1134	1.9308	1090.00	1.00
8	4-Cl	S	12.00	-1.0792	720.00	9.1134	1.9006	1114.00	1.00
9	3-Br	S	15.00	-1.1761	708.00	9.1134	1.9308	1090.00	1.00
10	3-F	S	12.00	-1.0792	720.00	9.1134	1.9066	1114.00	1.00
11	2-CN	S	9.10	-0.9590	708.00	9.1134	1.9308	1090.00	0.00
12	3-CN	S	1.10	-0.0414	802.00	9.6682	1.9826	1210.00	0.00
13	3-CF_3	S	7.10	-0.8513	850.00	9.6514	1.8718	1306.00	1.00
14	2,5-Cl_2	S	3.50	-0.5441	946.00	10.0241	1.9344	1428.00	1.00
15	3,5-$(CH_3)_2$	S	1.10	-0.0414	800.00	9.5241	1.9861	1223.00	0.00
16	3,5-Cl_2	S	0.12	0.9208	811.00	9.5072	1.9568	1245.00	1.00
17	3-Cl, 5-CH_3	S	1.70	-0.2304	811.00	9.5072	1.9568	1245.00	1.00
18	3-OCH_3, 5-CH_3	S	0.14	0.8539	811.00	9.5072	1.9568	1245.00	0.00
19	3-OCH_3, 5-CF_3	S	13.00	-1.1139	934.00	10.0453	1.9609	1420.00	1.00

Comp. No.	R	R'	IC_{50}	log $(1/IC_{50})$	W	χ	J	Sz	IPXR
20	2-OCH_3	SO	12.00	-1.0792	880.00	10.0958	2.0945	1316.00	0.00
21	3-OCH_3	SO	19.00	-1.2788	906.00	10.0789	2.0329	1368.00	0.00
22	3-CH_3	SO	10.00	-1.0000	782.00	9.5409	2.0410	1192.00	0.00
23	3-Br	SO	4.80	-0.6812	782.00	9.5409	2.0410	1192.00	1.00
24	2-CN	SO	9.90	-0.9956	880.00	10.0958	2.0945	1316.00	0.00
25	3,5-$(CH_3)_2$	SO	0.50	0.3010	890.00	9.9348	2.0672	1354.00	0.00
26	2,5-Cl_2	SO	6.20	-0.7924	878.00	9.9516	2.0978	1330.00	1.00
27	3-Cl, 5-CH_3	SO	0.52	0.2840	890.00	9.9348	2.0672	1354.00	1.00
28	3-OCH_3, 5-CF_3	SO	0.90	0.0458	1430.00	11.6841	2.1436	2116.00	1.00
29	H	SO_2	6.90	-0.8388	749.00	9.4804	2.1430	1133.00	0.00
30	2-OCH_3	SO_2	1.40	-0.1461	960.00	10.4291	2.2116	1424.00	0.00
31	3-OCH_3	SO_2	0.60	0.2218	988.00	10.4123	2.1476	1480.00	0.00
32	4-OCH_3	SO_2	13.00	-1.1139	1016.00	10.4123	2.0919	1536.00	0.00
33	2-CH_3	SO_2	4.50	-0.6532	844.00	9.8911	2.1936	1268.00	0.00
34	3-CH_3	SO_2	0.20	0.6990	858.00	9.8743	2.1568	1296.00	0.00
35	4-CH_3	SO_2	7.30	-0.8633	872.00	9.8743	2.1245	1324.00	0.00
36	2-Cl	SO_2	5.90	-0.7709	844.00	9.8911	2.1936	1268.00	1.00
37	3-Cl	SO_2	0.40	0.3979	858.00	9.8743	2.1568	1296.00	1.00
38	2-Br	SO_2	12.00	-1.0792	844.00	9.8911	2.1936	1268.00	1.00
39	3-Br	SO_2	0.20	0.6990	858.00	9.8743	2.1568	1296.00	1.00
40	2-F	SO_2	5.00	-0.6990	844.00	9.8911	2.1936	1268.00	1.00
41	2-CN	SO_2	6.00	-0.7782	960.00	10.4249	2.2116	1424.00	0.00
42	3-CN	SO_2	1.80	-0.2553	988.00	10.4123	2.1476	1480.00	0.00
43	3-CF_3	SO_2	5.30	-0.7243	1254.00	11.0856	2.1767	1854.00	1.00
44	2,5-Cl_2	SO_2	0.30	0.5229	958.00	10.2849	2.2148	1439.00	1.00
45	3,5-Cl_2	SO_2	0.03	1.5229	971.00	10.2681	2.1828	1465.00	1.00
46	3,5-$(CH_3)_2$	SO_2	0.01	2.1549	971.00	10.2681	2.1828	1465.00	0.00
47	3-Br, 5-CH_3	SO_2	0.00	2.5229	971.00	10.2681	2.1828	1465.00	1.00
48	3-Cl, 5-CH_3	SO_2	0.01	2.3010	971.00	10.2681	2.1828	1465.00	1.00
49	3-OCH_3, 5-CH_3	SO_2	0.01	2.0000	1106.00	10.8061	2.1840	1656.00	0.00
50	3-OCH_3, 5-CF_3	SO_2	0.04	1.3979	1535.00	12.0174	2.2510	2259.00	1.00
51	3-O $(CH_2)_3CH_3$,5-CH_3	SO_2	0.40	0.3979	1653.00	12.3061	2.1002	2371.00	0.00
52	1-Naphthyl	SO_2	1.00	0.0000	1207.00	11.4636	1.8154	2004.00	0.00
53	2-Naphthyl	SO_2	0.03	1.5229	1263.00	11.4467	1.7296	2116.00	0.00

Transformation of chemical structure into a mathematical graph makes it possible to express the chemical structure of these compounds by a single number. As is well known that a numerical index characterizing a molecule is called topological index. Therefore a topological index expresses topological information for a given chemical structure. A standard approach is to use hydrogen-suppressed graph defined as the graphs corresponding to the bare molecular skeleton. In the present study we have used carbon hydrogen suppressed molecular graph.

It is worthwhile to mention that the graphs here consist of one and the same cycle; they differ in the acyclic part only.

The advantage of topological indices is that they may be used directly as single number molecular descriptor in QSAR as well as QSPR. These relationships are mathematical models that enable the prediction of

properties and/or activities from structural parameters.

In the present study we have chosen 2-amino-6-arylsulfonyl benzonitriles (AASBN) because they exhibit interesting biological and chemical properties and may eventually lead to useful applications.

Several molecular modelling using uni as well as multivariate analyses are made using SYSTAT 10.0 version software[38]. First a correlation matrix is derived from the program and then regression analyses are done for obtaining several correlations. Results are summarized for comparison.

Topological indices used

All the four topological indices namely, Weiner index (W)[25], Randic connectivity index (χ)[31], Balaban index (J)[36] and Szeged index (Sz)[37] as described above are well presented in literature. Therefore they will be described here rather briefly.

The wiener index (W)

The Wiener index, W= W (G), of graph G is defined as the half sum of the element of distance matrix.

$$W = \tfrac{1}{2} \sum_{i=1} \sum_{j=1} (D_{ij}) \quad (1)$$

where (D_{ij}) is the ij^{th} element of the distance matrix, which denotes the shortest graph theoretical distance between vertices I and j in G. All graphs are hydrogen suppressed.

The randic connectivity index (χ)

The connectivity index, $\chi = \chi$ (G) of G is defined as:

$$\chi = \sum (d_i d_j)^{-0.5} \quad (2)$$

where d(i) and d(j) are the valencies of vertices I and j, equal to the number of bonds connected to the atoms I and j in G , representing the graph of a compound.

The balaban index (J)

The Balaban index J= J (G) of G is defined as:

$$J = M/\mu + 1\sum(d_i d_j)^{-1/2} \quad (3)$$

where M is number of bonds in G, μ is the cytomatic number of G and d_i & d_j (I or j = 1,2,3, N; is the number of vertices in G) are the distance sums.

The cytomatic number $\mu = \mu$ (G) of a polycyclic graph G is equal to the minimum number of edges necessary to be erased from G in order to transform it into the related to acyclic subgraph. In the case of monocyclic graph $\mu = 1$.

Although in many cases the values of μ are obvious for the complicated polygraph structure it can be calculated by means of the following expression.

$$\mu = M-n+1 \quad (4)$$

The distance sum (di) for an atom I of G represents a sum of all entries in the corresponding row (or column) of the distance matrix D.

$$Di = \sum (Dij) \quad (I = 1,2\ldots\ldots\ldots\ldots N) \tag{5}$$

The szeged index (Zz)

The Szeged index, Sz= Sz (g), of G is defined as:

$$Sz = Sz(G) = \sum_{u,v} n_u n_v \tag{6}$$

where summation goes over all edges (u, v) in a cyclic graph (G), n_u stands for the number of vertices nearer to the vertex v than u, n_v stands for the number of vertices nearer to the vertex u than v, The distance d (u, v) is the number of edges in a shortest path connectivity vertices V and U in G.

RESULTS AND DISCUSSION

The structural descriptors (W, J, χ, Sz and IPXR) of 2-amino-6-arylsulfonyl benzonitrile (AASBN) analogues are given in Table-1. The Table also records the IC_{50}, $\log(1/IC_{50})$ and the position of the substituents (R and R') on the benzene ring.

Recall that better results are obtained by introducing dummy parameter (IPXR) for the halogen substituents on the side chain R. The indicator parameter IPXR is taken as unity for electron-withdrawing (Cl, Br, F) substituents on R; otherwise, the values are zero. This indicator parameter is also recorded in Table-1. At this stage it is worth mentioning that the halogens exhibit a negative inductive effect *i.e.*, are electron withdrawing *via* the σ-bond.

The correlation matrix for the correlation of $\log(1/IC_{50})$ with the former mentioned structural descriptors (topological indices) of AASBN derivatives are shown in Table-2.

TABLE-2
CORRELATION MATRIX OF $\log(1/IC_{50})$ OF 2-AMINO-6-ARYLSULFONYLBENZONITRILE ANALOGUES WITH STRUCTURAL DESCRIPTORS, W, J, χ, Sz,, IPX (n=32)

	$\log(1/IC_{50})$	W	χ	J	Sz	IPXR
$\log(1/IC_{50})$	1.000					
W	0.700	1.000				
χ	0.700	0.979	1.000			
J	0.216	0.260	0.304	1.000		
Sz	0.726	0.987	0.978	0.144	1.000	
IPXR	-0.198	-0.160	-0.234	-0.081	-0.172	1.000

The regression parameters as well as the quality of various uni- and multivariate correlations are summarized in Table-3.

The $\log(1/IC_{50})$ values for the AASBN derivatives are estimated using the best multivariate correlation. Such estimated $\log(1/IC_{50})$ values are re

TABLE-3
REGRESSION PARAMETERS AND QUALITY OF CORRELATION OF $\log(1/IC_{50})$ WITH STRUCTURAL DESCRIPTORS FOR 2-AMINO-6-ARYLSULFONYLBENZONITRILES (N = 32)

S. No.	Correlation Parameter	A_i i = 1-5	B	SD	Multi R	R^2	R^2_{Adj}	F-ratio	Q^2
1	W	A1 = 0.002	-2.492	0.540	0.700	0.490	0.473	28.843	0.490
2	χ	A1 = 0.608	-6.501	0.540	0.700	0.490	0.473	28.811	0.490
3	J	A1 = 1.244	-2.950	0.738	0.216	0.047	0.015	1.464	0.047
4	Sz	A1 = 0.002	-2.600	0.520	0.726	0.527	0.511	33.393	0.527
5	W, IPX	A1 = 0.002 A2 = -0.130	-2.393	0.545	0.706	0.498	0.463	14.372	0.498
6	χ, IPX	A1 = 0.601 A2 = -0.054	-6.403	0.548	0.701	0.491	0.456	13.995	0.491
7	J, IPX	A1 = 1.158 A2 = -0.268	-2.660	0.737	0.282	0.079	0.016	1.251	0.079
8	Sz, IPX	A1 = 0.002 A2 = -0.111	-2.512	0.526	0.730	0.532	0.500	16.503	0.532
9	W, χ, IPX	A1 = 0.002 A2 = 0.191 A3 = -0.105	-3.684	0.553	0.707	0.500	0.446	9.316	0.500
10	W, J, IPX	A1 = 0.002 A2 = 0.185 A3 = -0.129	-2.745	0.554	0.706	0.499	0.445	9.287	0.499
11	W, Sz, IPX	A1 = -0.002 A2 = 0.003 A3 = -0.103	-2.522	0.530	0.735	0.541	0.492	10.998	0.541
12	χ, J, IPX	A1 = 0.600 A2 = 0.017 A3 = -0.054	-6.429	0.558	0.701	0.491	0.437	9.009	0.491
13	χ, Sz, IPX	A1 = -0.321 A2 = 0.002 A3 = -0.148	-0.359	0.532	0.733	0.538	0.488	10.856	0.538
11	J, Sz, IPX	A1 = 0.631 A2 = 0.002 A3 = -0.102	-3.750	0.528	0.738	0.544	0.495	11.135	0.544
15	W, χ, J, IPX	A1 = 0.002 A2 = 0.166 A3 = 0.131 A4 = -0.107	-3.763	0.563	0.707	0.500	0.426	6.750	0.500
16	W, χ, Sz, IPX	A1 = -0.001 A2 = -0.173 A3 = 0.003 A4 = -0.125	-1.360	0.539	0.736	0.542	0.474	7.994	0.542
17	W, J, Sz, IPX	A1 = -0.008 A2 = 2.260 A3 = 0.006 A4 = -0.043	-6.980	0.498	0.781	0.609	0.552	10.531	0.609
18	χ, J, Sz, IPX	A1 = -2.042 A2 = 2.842 A3 = 0.006 A4 = -0.304	5.612	0.491	0.787	0.619	0.563	10.986	0.614
19	W, χ, J, Sz,	A1 = -0.012 A2 = -2.518 A3 = 0.001 A4 = -0.321	2.350	0.415	0.854	0.729	0.689	18.163	0.729
20	W, χ, J, Sz, IPX	A1 = -0.012 A2 = -3.161 A3 = 6.672 A4 = 0.017 A5 = -0.321	5.547	0.393	0.875	0.766	0.721	17.010	0.766

TABLE-4
ESTIMATED AND OBSERVED log IC_{50} VALUES OF 2-AMINO-6-ARYLSULFONYLBENZONITRILES ANALOGUES DERIVED FROM THE REGRESSION Eq.7

$Log(1/IC_{50})= -0.012(\pm0.003)\ W - 3.161(\pm0.758)\chi + 6.672(\pm1.339)\ J + 0.017(\pm0.003)\ Sz - 0.321(\pm0.159)\ IPX + 5.547\ (\pm3.427)$

Comp. No.	$log(1/IC_{50})$ (Obsd)	$log(1/IC_{50})$ (estd)	Residual = $log(1/IC_{50})$ (Obsd)- $log(1/IC_{50})$ (estd)
1	-0.9395	-0.7779	-0.1616
2	-0.4314	-1.1702	0.7388
3	-0.7559	-0.5430	-0.2129
4	-0.8573	-1.0414	0.1841
5	-1.2041	-0.9600	-0.2441
6	-1.0792	-0.9037	-0.1755
7	-1.1761	-0.9600	-0.2161
8	-1.0792	-0.8637	-0.2155
9	-0.9590	-0.6394	-0.3197
10	-0.8513	-1.1457	0.2944
11	-0.5441	-1.0195	0.4754
12	-0.0414	-0.4487	0.4073
13	-0.2305	-0.6751	0.4446
14	-1.1139	-0.8987	-0.2153
15	-1.0792	-0.9392	-0.1399
16	-1.2788	-0.7382	-0.5405
17	-1.0000	-0.4382	-0.5618
18	-0.6812	-0.7589	0.0776
19	-0.9956	-0.9392	-0.0564
20	0.3010	-0.0953	0.3963
21	-0.7924	-0.5226	-0.2698
22	-0.1461	-0.3662	0.2201
23	0.2218	-0.1384	0.3602
24	0.6990	0.1074	0.5915
25	-0.6990	-0.3220	-0.3770
26	-0.7782	-0.3530	-0.4252
27	-0.2553	-0.1384	-0.1169
28	0.5228	0.0663	0.4566
29	1.3979	1.6176	-0.2197
30	0.3979	0.4711	-0.0732
31	0.0000	0.4726	-0.4726
32	1.5228	1.1565	0.3664

corded in Table-4. The observed (experimental) $log(1/IC_{50})$ values are also given in Table-4. The quality of correlations is demonstrated by the residual values, *i.e.*, the difference between observed and estimated $log(1/IC_{50})$ values. The residual obtained from the best correlation are also given in Table-4.

A perusal of the correlation matrix (Table-2) and the regression parameters recorded in Table-3 show that in univariate correlations W, Sz, and χ are equally capable of predicting the biological activity of the AASBN derivatives while J poorly correlates with $log(1/IC_{50})$. Sz gives slightly

better results than both W and χ while J gives comparatively poor result than the other indices.

The correlation matrix in Table-2 also indicate, of the four indices considered in the study, three are highly linearly related, in particular, χ, W and Sz are proportional. The data shows that of all the correlations, correlation of Sz with W is slightly better.

The parameters recorded in Table-3 indicate that the correlation of the $\log(1/IC_{50})$ values of AASBN derivatives is improved by introducing indicator parameters (IPXR) as well as by using multiple linear regression analysis. We tried several multiple correlations, and the results are given in Table-3.

Of all the possible correlations (uni, and bi-variate) W and χ have shown competitive results even when used with indicator parameters while Sz give better results and J again correlates poorly.

It is noted that by introducing IPXR in the multivariate correlation the quality of the correlation is considerably improved. The use of IPXR has resulted in the lowering of standard deviation as well as in an appreciable increase in the correlation coefficient.

The perusal of Table-3 shows that the quality of higher correlations is improved compared to both uni and bivariate correlations. The correlation coefficient in all these higher multiple correlations are found to be above 0.700.

The data presented in Table-3 indicate that use of all the five parameters, *viz.*, W, χ, J, Sz, IPXR, give the best results. This correlation has compounds number 3, 4, 12, 16, 18, 27, 28, 29, 32, 33, 35, 36, 37, 38, 39, 43, 45, 46, 47, 48 and 49 as outliers. Neglecting these compounds give the best correlation with correlation coefficient of the magnitude of 0.875. Therefore using the corresponding regression parameters from Table-3, the following regression expression can be proposed which can be subsequently used to estimate $\log(1/IC_{50})$ of AASBN derivatives:

$$\log(1/IC_{50}) = -0.012(\pm0.003)\,W - 3.161(\pm0.758)\chi + 6.672(\pm1.339)\,J + 0.017(\pm0.003)\,Sz - 0.321(\pm0.159)\,IPX + 5.547\,(\pm3.427) \quad (7)$$

It is also noted that the low standard deviation 0.393 and high correlation coefficient (Multiple-R) 0.875, quality of correlation (Q^2) 0.766 and F-ratio (17.010) indicate that out of all the correlations we tried (Table-3) the aforementioned correlation (Eq.7) gives the best estimated values for $\log(1/IC_{50})$.

To confirm our findings we have estimated $\log(1/IC_{50})$ values for 2-amino-6-arylsulfonylbenzonitrile derivatives using Equation 7. These values are shown in Table-4. A comparison of these estimated values of $\log(1/IC_{50})$ with the observed ones as well as the magnitude of the residues

between observed and estimated log(1/IC_{50}) values confirm the above findings.

The aforementioned results and discussion indicate that the recently developed Sz index and the old Randic connectivity index χ, as well as Weiner index W have similar correlation potentials. Thus, W, Sz and χ are better indices than J in QSAR studies; however Sz gives better results than W and χ.

Conclusion

The present study related to 2-amino-6-arylsulfonylbenzonitrile derivatives leads us to make the following conclusions: (1) The indices W, Sz, and χ for 2-amino-6-arylsulfonylbenzonitrile derivatives are all highly linearly related; W, χ and Sz are proportional while J has lesser correlating potential in this case of QSAR study. (2) The correlation of W with Sz is better than the corresponding correlation related to χ and J indices. (3) In monoparametric correlations log(1/IC_{50}) values of 2-amino-6-arylsulfonylbenzonitrile derivatives correlate equally well with W, Sz, and χ and Sz gives slightly better correlation than W and χ while J correlates still poorly. (4) The recently developed Szeged index can also be successfully used in developing QSPR as well as QSAR. (5) Best results are obtained by adding the indicator parameter and by employing multiple linear regression analysis and (6) negative coefficient of IPXR (indicator parameter) indicates presence of halogen atom on the side chain is adversely affecting the IC_{50} values.

REFERENCES

1. E. De Clercq, *Rev. Med. Virol.*, **6**, 97 (1996).
2. E. De Clercq, *IL Farmaco*, **54**, 26 (1999).
3. G. Campiani, A. Ramunno, G. Maga, V. Nacci, C. Fattorusso, B. Catalanotti, E. Morelli and E. Novellino, *Curr. Pharm. Des.*, **8**, 615 (2002).
4. J.P. Kleim, R. Bender, U. M. Billhardt, C. Meichsner, G. Riess, M. Rosner, I. Winkler and A. Paessens, *Antimicrob. Agents Chemother.*, **37**, 1659 (1993).
5. M. Baba, H. Tanakas, E. De Clercq, R. Pauwels, J. Balzarini, D. Schols, H. Nakashima, C.F. Perno, R.T. Walker and T. Miyasaka, *Biochem. Biophys. Res. Commun.*, **165**, 1375 (1989).
6. J. Balzarini, M.J.P.-Pérez, A.S.-Felix, D. Schols, C.F. Perno, A. Vandamme, M.J. Camarasa and E. De Clercq, *Proc. Natl. Acad. Sci. (USA)*, **89**, 4392 (1992).
7. R. Pauwels, K. Andries, Z. Debyser, P. Van Daele, D. Schols, A.M. Vandamme, C. G. Janssen, J. Anne, G. Cauwenbergh, J. Desmyter, J. Heykants, M.A.C. Janssen, E. De Clercq and P.A.J. Janssen, *Proc. Natl. Acad. Sci. (USA)*, **90**, 1711 (1993).
8. C. Ahgren, K. Backro, F.W. Bell, A.S. Cantrell, M. Clemens, J.M. Colacino, J.B. Deeter, J.A. Engelhardt, M. Hogberg, S.R. Jaskunas and N.G. Johanssons, *Antimicrob. Agents Chemother.*, **39**, 1329 (1995).
9. R. Pauwels, K. Andries, J. Desmyter, D. Schols, M.J. Kukla, H.J. Breslin, A. Raeymaeckers, J. Van Gelder, R. Woestenborghs and J. Heykants, *Nature*, **343**, 470 (1990).

10. V.J. Merluzzi, K.D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J.C. Wu, C.K. Shih, K. Eckner, S. Hattox and J. Adams, *Science*, **250**, 1411 (1990).
11. D.L. Romero, M. Busso, C.K. Tan, F. Reusser, J.R. Palmer, S.M. Poppe, P.F. Aristoff, K.M. Downey, A.G. So, L. Resnick and W.G. Tarpley, *Proc. Natl. Acad. Sci. (USA)*, **88**, 8806 (1991).
12. G.Z. Xian, Q.Y. Dong, Z. Li, E.J. Arts and M.A. Wainberg, *J. Bio. Chem.*, **270**, 31046 (1995).
13. H. Jonckheere, J. Anne and E. De Clercq, *Medicin. Res. Rev.*, **20**, 129 (2000).
14. E. Arnold, K. Das, J. Ding, P.N. Yadav, Y. Hsiou, P.L. Boyer and S.H. Hughes, *Drug Des. Discov.*, **13**, 29 (1996).
15. P.P. Mager, *Med. Res. Rev.*, **17**, 235 (1997).
16. D. Richman, C.K. Shih, I. Lowy, J. Rose, P. Prodanovich, S. Goff and J. Griffin, *Proc. Natl. Acad. Sci. (USA)*, **88**, 11241 (1991).
17. J.H. Chan, *J. Med. Chem.*, **44**, 1866 (2001).
18. B. Lucic, S. Nikolic, N. Trinajstic, D. Juretic and A. Juric, *Croat. Chim. Acta*, **68**, 435 (1995).
19. B. Lucic, S. Nikolic, N. Trinajstic, A. Juric and Z. Mihalic, *Croat. Chim. Acta*, **68**, 417 (1995).
20. M. Randic and P.G. Seybold, *SAR-QSAR Environ. Res.*, **1**, 77 (1993).
21. M. Randic, *J. Math. Chem.*, **9**, 97 (1992).
22. N. Trinajstic, Chemical Graph Theory, CRC Press: Boca Raton, FL, Vols. 1 and 2 (1983).
23. P.G. Seybold, M. May and U.A. Bagal, *J. Chem. Educ.*, **64**, 575 (1987).
24. I. Gutman and O.E. Polansky, Mathematical Concepts in Organic Chemistry; Springer-Verlag, Berlin (1989).
25. H. Wiener, *J. Am. Chem. Soc.*, **69**, 17 (1947).
26. R.E. Merrifield and H. E. Simmons, Topological Methods in Chemistry; Wiley, New York (1989).
27. R.B. King, Chemical Applications of Topology and Graph Theory; Elsevier: Amsterdam (1987).
28. R.B. King and D.H. Rouvray, Graph Theory and Topology in Chemistry; Elsevier, Amsterdam (1987).
29. N. Trinajstic, A. Sabijic and S. Nikolic, *Acta. Pharm. Jugosal.*, **36**, 1 (1986).
30. N. Trinajstic, S. Nicolic and S. Carter, *Kem. Ind. (Zegreb)*, **38**, 469 (1989).
31. M. Randic, *J. Am. Chem. Soc.*, **97**, 6609 (1975).
32. M. Randic, *J. Chem. Inf. Comput. Sci.*, **31**, 311 (1991).
33. M. Randic, *New J. Chem.*, **18**, 517 (1991).
34. Z. Mihalic, S. Nikolic and N. Trinajstic, *J. Chem. Inf. Comput. Sci.*, **32**, 28 (1992).
35. D. Bonchev, Information Theoretic Indices for Characterization of Chemical Structures; Research Studies Press: Chichester (1983).
36. A.T. Balaban, *Chem. Phys. Lett.*, **80**, 399 (1982).
37. A.A. Dobrynin and I. Gutman, *Pib. De L'inst. Math.*, **56**, 18 (1994).
38. M. Mandloi, A. Sikarwar, N.S. Sapre, S. Karmakar and P.V. Khadikar, *J. Chem. Inf. Comput. Sci.*, **40**, 57 (2000).
39. SYSTAT 10.0 SYSTAT Software Inc. USA.

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